EXHIBIT 6i

Gustavson 2021

This study is a longitudinal sibling control study that examined the association between APAP use during pregnancy and offspring ADHD.[428] The sibling control model, also known as the sibling comparison design or within-family design, is a research approach used in epidemiological and genetic studies to compare outcomes between siblings within the same family.

Exposure: The exposure of interest in this study was maternal APAP use during pregnancy. Information on APAP use was obtained from maternal self-reported questionnaires. This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: The outcome of interest in this study was ADHD diagnosis in the offspring. ADHD diagnoses were obtained from the Norwegian Patient Registry.

Control group: This study used a sibling control design, where siblings discordant for prenatal APAP exposure were compared regarding risk of having an ADHD diagnosis.

Study size: The study included 26,613 children from 12,902 families participating in the prospective Norwegian Mother, Father, and Child Cohort Study (MoBa).

Confounding factors or biases and how or if they were controlled: The study adjusted for several potential confounding factors, including maternal age, parity, child's sex, maternal education level, smoking status, alcohol use, and symptoms of depression and anxiety. Additionally, the study used propensity score matching to control for potential confounding by indication.

Limitations: Only discordant siblings contribute informative data in the sibling design. In this study, 623 mothers participated with children discordant on outcome, 306 mother participated with children that were discordant on exposure as well as outcome. 380 mothers participated with children discordant on the exposure for 29 days or more, and only 34 of these had children discordant on outcome. The authors indicate that the "statistical power to detect within effects was relatively low."

While the sibling control design allows for the control of unmeasured familial confounding factors, it may also control for potential mediating factors that affect all siblings, even if only one is exposed. This may lead to underestimation of association estimates. Sibling control models do not control for confounders that are not shared between siblings, and this can also introduce bias in the study.

Having an initial child with ADHD may affect the decision and timing of having more children, and this may have biased the current results. The order of the siblings was not reported to examine this impact. The sibling order has been reported to have an impact on diagnosis of ADHD or ASD in a sibling. For example, a separate study supported a relatively greater impact of within-diagnosis sibling recurrence risk and sibling cross-aggregation of ADHD and ASD among later-born siblings of children with either disorder.[429] Specifically, the study found that later-born siblings of children with ASD or ADHD appear

[428] Gustavson et al. 2021. Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder – a longitudinal sibling control study. JCPP Advances. 2021;e12020. DOI: 10.1002/jcv2.12020

[429] Carey et al. Examining associations between prenatal biomarkers of oxidative stress and ASD-related outcomes using quantile regression. J Autism Dev Disord. 2022 Jun 9:10.1007/s10803-022-05625-9. doi: 10.1007/s10803-022-05625-9. Epub ahead of print. PMID: 35678944; PMCID: PMC9732143.

to be at elevated risk for the same disorder and of being diagnosed with the other disorder. Compared with later-born siblings of children without ADHD or ASD, later-born siblings of children with ASD were more likely to be diagnosed with ASD (odds ratio (OR), 30.38; 95% CI, 17.73-52.06) or ADHD in the absence of ASD (OR, 3.70; 95% CI, 1.67-8.21). Compared with later-born siblings of children without a diagnosis, later-born siblings of children with ADHD were more likely to be diagnosed with ADHD (OR, 13.05; 95% CI, 9.86-17.27) or ASD in the absence of ADHD (OR, 4.35; 95% CI, 2.43-7.79). These findings indicate that having a sibling previously diagnosed with ADHD or ASD increased the risk more for the second child.

Results: This study found that children exposed to acetaminophen up to 28 days during pregnancy did not have an increased risk of receiving an ADHD diagnosis compared to unexposed children. However, long-term exposure (29 days or more) was associated with a two-fold increase in risk of ADHD diagnosis (adjusted hazard ratio (aHR) = 2.02, 95% CI = 1.17–3.25). All children (both exposed and unexposed) born to a mother with long-term use of acetaminophen in one pregnancy, had increased risk of receiving an ADHD diagnosis compared to children of mothers who did not use acetaminophen in any pregnancy (aHR = 2.77, 995% CI = 1.48–5.05). In the sibling control model, the association between long-term acetaminophen use and ADHD in the child was no longer present (aHR = 1.06, 995% CI = 0.51–2.05). This indicates that the observed association between long-term acetaminophen use during pregnancy and ADHD in the child may at least partly be confounded by unobserved family factors.

The study reported that both the exposed and the unexposed children of mothers with long-term use of APAP in one of the pregnancies had increased risk of receiving an ADHD diagnosis. This indicates that the observed association between long-term acetaminophen use during pregnancy and ADHD in the child may at least partly be confounded by unobserved family factors.

Liew 2014

Study type: The study was a prospective observational cohort study.[430]

Information used to determine exposure: Acetaminophen use during pregnancy was assessed via 3 computer-assisted telephone interviews during pregnancy and 6 months after childbirth.

Outcome definition and determination: The main outcomes measured were the risk of receiving an hyperkinetic disorder (HKD) diagnosis, using ADHD medications, or having ADHD-like behaviors at age 7 years after prenatal exposure to acetaminophen. Behavioral outcomes were determined Strengths and Difficulties Questionnaire (SKD).

Study size: The study included 64,322 live-born children and mothers enrolled in the Danish National Birth Cohort during 1996-2002 for the HKD analysis. They further excluded children whose caregiver did not respond to a self-administered online/mail questionnaire when the child turned 7 years, resulting in 40,916 for children for the SKD.

Confounding factors or biases and how or if they were controlled: To address potential confounding by indication, they used stratified analyses according to self-reported episodes of fever, inflammation, or infection during pregnancy. Other potential confounders included the birth year of the child, birth weight,

[430] Liew et al. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. JAMA Pediatr. 2014 Apr;168(4):313-20. doi: 10.1001/jamapediatrics.2013.4914. PMID: 24566677.

and sex, as well as maternal age, parity, gestational age at delivery, socioeconomic status, smoking and alcohol consumption during pregnancy, prepregnant body mass index, and maternal self-reported psychiatric illnesses. Women were asked to self-report if they had psychiatric illnesses and had sought medical or psychological help for depression, anxiety, childhood psychiatric disorder, family problems/life crisis, or other mental health problems. Parents provided self-reported childhood behavior problems (SDQ scale) were considered for analyzing ADHD-like behaviors in children. Other potential confounders such as age of father at the birth of the child, Apgar scores, and season of conception were evaluated but did not significantly affect the effect estimates (<1% change) and were not included in the final models.

Limitations: The inability to accurately assess dosage or number of pills taken and the lack of specific information on the gestational week of APAP use affected the precision of effect estimation. However, the authors reported that excluding these cases when assessing exposure duration did not alter the results or conclusions. Flawed recall of drug names, frequency, and timing of use is likely to be nondifferential in relation to the disease status of the child, resulting in bias towards the null and underestimated effects.

Results: Maternal acetaminophen use during pregnancy was associated with a higher risk of children receiving a hospital diagnosis of HKD (hazard ratio = 1.37; 95% CI, 1.19-1.59), use of ADHD medications (hazard ratio = 1.29; 95% CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (risk ratio = 1.13; 95% CI, 1.01-1.27). The associations were stronger with use in multiple trimesters and showed an exposure-response trend with increasing frequency of acetaminophen use during gestation. The results were not confounded by maternal inflammation, infection during pregnancy, the mother's mental health problems, or other potential confounders examined.

The authors conclude that prenatal exposure to APAP increased the risk of children receiving a hospital diagnosis of HKD or ADHD medication and exhibiting ADHD-like behaviors. The risk increased with higher frequency of APAP use in an exposure-response manner. These associations support APAP as a contributor to the increasing incidence of HKD/ADHD.

Liew 2016b

This is a prospective cohort study that followed mothers and children from pregnancy to age 5.[431]

Information used to determine exposure: Exposure to paracetamol was determined by self-reported use in three telephone interviews conducted at gestational weeks 12 and 30 and 6 months postpartum.

Outcome definition and determination: The outcomes were attention and executive function in children at age 5, measured by the Test of Everyday Attention for Children at Five (TEACh-5) and the Behaviour Rating Inventory of Executive Function (BRIEF), completed by trained psychologists, parents and preschool teachers.

Control group: The control group consisted of mothers who never used paracetamol during pregnancy.

[431] Liew et al. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. Int J Epidemiol. 2016 Dec 1;45(6):2009-2017. doi: 10.1093/ije/dyw296. PMID: 28031314.

Study size: The study included 1491 mother-child pairs who completed all three telephone interviews and participated in the neuropsychological assessment at age 5.

Confounding factors or biases and how or if they were controlled: The study adjusted for potential confounders such as parental education, maternal IQ, maternal mental health, prenatal smoking and drinking, parity, maternal age, child's sex, maternal pre-pregnancy BMI, maternal musculoskeletal diseases, fever or infection/inflammation during pregnancy, and maternal use of ibuprofen or aspirin. The study also used inverse probability weights to account for subject selection and non-participation. However, the study acknowledged that residual confounding or unmeasured confounding may still exist, such as genetic factors, environmental exposures, or other medications.

Limitations: The study had several limitations, such as the reliance on self-reported paracetamol use, the lack of information on dose and timing of exposure, the possibility of recall bias or misclassification of exposure, the potential influence of reverse causation or indication bias, the generalizability of the findings to other populations or settings, and the uncertainty of the biological mechanisms underlying the observed associations.

Results: First-trimester APAP use was associated with poorer attention scores in childhood (mean difference -0.34, 95% CI -0.63, -0.05 for overall attention; -0.25, 95% CI -0.50, 0.01 for selective attention). Prenatal exposure to APAPl increased the risk of subnormal overall attention (OR 1.5, 95% CI 1.0-2.5), selective attention difficulties (OR 1.5, 95% CI 1.0-2.4), and parent-rated subnormal executive function (metacognition index, OR 1.5, 95% CI 0.9-2.3). Longer duration of APAP use in pregnancy further elevated the risks for subnormal overall attention or executive function.

In conclusion, this study provides evidence of a moderate association between prenatal APAP use and subnormal attention and executive function in offspring at age 5. This study provides additional support for the interaction of *in utero* exposure of APAP on adverse neurodevelopment in children.

Liew 2019

This is a prospective cohort study design using samples selected from the Nurses' Health Study II cohort.[432]

Information used to determine exposure: Information about acetaminophen exposure was based on self-reported acetaminophen use at the time of pregnancy and during two negative control exposure periods (about 4 years before and 4 years after the pregnancy). This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: The outcome of interest was childhood attention-deficit/hyperactivity disorder. ADHD diagnoses were obtained from maternal report.

Control group: The control group consisted of children without attention-deficit/hyperactivity disorder diagnosis.

[432] Liew et al. Use of Negative Control Exposure Analysis to Evaluate Confounding: An Example of Acetaminophen Exposure and Attention-Deficit/Hyperactivity Disorder in Nurses' Health Study II. Am J Epidemiol. 2019 Apr 1;188(4):768-775. doi: 10.1093/aje/kwy288. PMID: 30923825; PMCID: PMC6438812.

Study size: The study included a total of 8,856 children born in 1993–2005 to women enrolled in the Nurses' Health Study II cohort. ADHD was reported in 721 children, versus 8,135 without ADHD.

Confounding factors or biases and how or if they were controlled: Potential covariates such as maternal age, race/ethnicity, education, marital status, pre-pregnancy body mass index, smoking during pregnancy, alcohol use during pregnancy, and child sex were included in the statistical model.

Limitations: Reported limitations included the possibility of unmeasured confounding factors specific to pregnancy, lack of detailed information on timing and dosage of acetaminophen use, potential misclassification of exposure, inability to explore dose-response relationships, lack of data on prescription medication use as a confounder, reliance on self-reported ADHD diagnoses without clinical verification, and reliance on maternal reports, although they are generally reliable.

Results: Only APAP use at the time of pregnancy was associated with childhood ADHD (OR = 1.34, 95% CI: 1.05-1.72), and the effect estimates for the two negative control exposure periods (about 4 years before and 4 years after the pregnancy) were null.

The authors conclude that the longitudinal data from the NHS II allowed for comparisons across different time periods, supporting previous findings of a link between prenatal APAP exposure and neurodevelopmental outcomes.

Thompson 2014

This is a longitudinal cohort study design using samples selected from the Auckland Birthweight Collaborative Study.[433]

Information used to determine exposure: Information about acetaminophen exposure was based on self-reported drug use during pregnancy (acetaminophen, aspirin, antacids, and antibiotics). This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: Symptoms of ADHD were measured at ages 7 and 11 using the parent format of the Strengths and Difficulties Questionnaire (SDQ) and also using the child format at age 11. ADHD symptoms were also measured with more specificity using the Conners' Behavioural Rating Scale: Revised (CRS:R) parent report at ages 7 and 11 years.

Control group: The control group consisted of children whose mothers did not use acetaminophen during pregnancy.

Study size: The study included a total of 871 infants of European descent sampled disproportionately for small for gestational age.

[433] Thompson et al. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. PLoS One. 2014 Sep 24;9(9):e108210. doi: 10.1371/journal.pone.0108210. PMID: 25251831; PMCID: PMC4177119.

Confounding factors or biases and how or if they were controlled: Potential covariates such as maternal age, education, smoking during pregnancy, alcohol use during pregnancy, and child sex were included in the statistical model.

Limitations: Study limitations included the lack of information on the dosage and trimester of APAP use during pregnancy. Unmeasured environmental factors and potential epigenetic influences may also affect disease risk and neurological outcomes. Additionally, the follow-up rate was low (59-70%), but the percentages of small for gestational age and appropriate for gestational age remained the same. The study also reported limited generalizability to European populations, and potential selection bias due to parental ADHD status should be considered.

Results: Acetaminophen was used by 49.8% of the study mothers during pregnancy. There were significantly higher total scores on all 3 SDQ formats is APAP was used during pregnancy, but there were no significant differences associated with any of the other drugs.

The authors conclude that these findings strengthen the relationship between *in utero* APAP exposure and ADHD in offspring.

Ystrom 2017

This is a cohort study using samples selected from the Norwegian Mother and Child Cohort Study and examines the association between acetaminophen exposure and ADHD diagnosis.[434]

Information used to determine exposure: The authors used self-report questionnaires from the mothers and fathers to obtain information on APAP use for each medical condition and each exposure window before and during pregnancy. They also used the Anatomic Therapeutic Chemical Classification System to classify and group medication exposure.

Outcome definition and determination: The outcome of interest was ADHD diagnosis in offspring, which was obtained from the Norwegian Patient Registry that records individual-level diagnoses from government-owned and government-financed hospitals and outpatient clinics.

Control group: The control group consisted of children who were not diagnosed with ADHD and whose parents did not use acetaminophen before or during pregnancy.

Study size: The study population included 112973 children, of whom 2246 had been diagnosed with ADHD by December 31, 2014.

Confounding factors or biases and how or if they were controlled: The authors considered several potential confounders, such as parental symptoms of ADHD, maternal alcohol use, smoking, anxiety, depression, education, marital status, BMI, age, parity, birth year, and 128 medical conditions indicative of acetaminophen use. They adjusted for these factors in their Cox proportional hazard models and stratified their analyses by each indication of use. They also used maternal preconceptional use and paternal preconceptional use as negative controls to test the specificity of the gestational effect.

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[434] Ystrom et al. Prenatal Exposure to Acetaminophen and Risk of ADHD. Pediatrics. 2017 Nov;140(5):e20163840. doi: 10.1542/peds.2016-3840. PMID: 29084830; PMCID: PMC5654387.

Limitations: The authors acknowledged some limitations of their study, such as possible residual confounding by unmeasured factors (e.g., severity of indications, genetic factors), lack of validation of the ADHD diagnosis in a research clinic, and potential selection bias due to underrepresentation of young parents and smokers in the cohort.

Results: The HR for one trimester showed a non-significant association (HR = 1.07; 95% CI 0.96-1.19), while the HR for two trimesters indicated a significant association (HR = 1.22; 95% CI 1.07-1.38). Three trimesters showed a non-significant association (HR = 1.27; 95% CI 0.99-1.63). Maternal APAP use for all indications, for more than 29 days had a higher HR of 2.20 (95% CI 1.50-3.24). However, use for less than 8 days had a negative association with ADHD (HR = 0.90; 95% CI 0.81-1.00). APAP use for fever and infections, for 22 to 28 days showed a strong and significant association with ADHD (HR = 6.15; 95% CI 1.71-22.05).

The study concludes that long-term maternal APAP use during pregnancy is associated with ADHD in offspring, even after adjusting for confounders. Only use during pregnancy, not preconceptional use, showed an association with ADHD. Paternal use was also associated with the ADHD. The authors assumed this association was not biological. It appears they were unaware of the NTP (1993) study[435] and reviewed Ofirmev (IV APAP) label, see page 121 above, which indicates "increased percentage of abnormal sperm" in treated animals. Likewise, they may have also been unaware of a lab at the NIH reporting, also in November of 2017, a significant increase in % DNA fragmentation of sperm in men with high urinary APAP.[436]

Weight of the Evidence for the Association of APAP with ADHD

As indicated above, there is a considerable body of evidence supporting the association between prenatal APAP exposure and an increased risk of neurodevelopmental disorders such as ADHD and ASD in children. These studies are generally consistent in their findings, with most reporting a positive association between prenatal APAP exposure and adverse neurodevelopmental outcomes. The studies also employed various study designs, including prospective cohort studies and case-control studies, which strengthens the evidence base. However, it is important to note that most of these studies relied on maternal self-reported acetaminophen use during pregnancy, which may be subject to recall bias or measurement error. Additionally, many of these studies did not account for potential confounding factors such as underlying medical conditions that may have prompted acetaminophen use during pregnancy.

Overall, the studies above should be categorized as **"some evidence" that taking APAP during pregnancy causes developmental toxicity**, this conclusion is based upon prenatal APAP exposure and a significantly increased risk of ADHD and ASD in children.

Based on the totality of studies reviewed above and as summarized below, prenatal exposure to APAP is associated with an increased risk of ADHD or ADHD-like symptoms in children. The strength of association varies depending on the dose, duration, timing, and indication of APAP use during pregnancy. Regarding dose, "therapeutic" dosages are sufficient to cause harm. Regarding duration, a longer duration

[435] National Toxicology Program. NTP Toxicology and Carcinogenesis Studies of Acetaminophen (CAS No. 103-90-2) in F344 Rats and B6C3F1 Mice (Feed Studies). Natl Toxicol Program Tech Rep Ser. 1993 Jan;394:1-274. PMID: 12637965.
[436] Smarr et al. Male urinary paracetamol and semen quality. Andrology. 2017 Nov;5(6):1082-1088. doi: 10.1111/andr.12413. Epub 2017 Aug 29. PMID: 28853221.

increases risk, with a 2.02-6.15 fold increase in risk reported for three to four weeks of exposure. Some studies also found no significant association or a negative association between APAP exposure and ADHD outcomes, this included the sibling control model, which was reportedly underpowered by the authors. **There is a moderate association between APAP use during pregnancy and ADHD in children.** More specifically, multiple independent studies reported a significant association between APAP exposure and increased risk of ADHD or ADHD-like symptoms. The data from these studies are summarized below:

Study	Exposure	Outcome	Findings
Anand 2021	Cord blood acetaminophen >50th percentile	ADHD diagnosis	2.10 (95% CI 1.43, 3.11)
Baker 2020	Detection of acetaminophen in meconium	ADHD	2.43 (95% CI, 1.41-4.21)
Baker 2020	Doubling of exposure	ADHD	1.10 (95% CI 1.02-1.19)
Chen 2019	Acetaminophen exposure in the second trimester	ADHD in offspring	1.19 (95% CI 1.00-1.40)
Chen 2019	Acetaminophen exposure in the first and second trimester	ADHD in offspring	1.28 (95% CI 1.00-1.64)
Chen 2019	Acetaminophen exposure in any trimester	ADHD in offspring	1.20 (95% CI 1.01-1.42)
Ji 2018	Below median maternal acetaminophen burden	ADHD diagnosis	1.58 (95% CI 1.02-2.46)
Ji 2018	Above median maternal acetaminophen burden	ADHD diagnosis	1.88 (95% CI 1.18, 3.00)
Gustavson 2021	Long-term exposure (29 days or more) to acetaminophen during pregnancy	ADHD diagnosis	2.02 (95% CI = 1.17–3.25)
Liew et al.,2014a	Maternal APAP use during pregnancy	HKD diagnosis, use of ADHD medications, or having ADHD-like behaviors at age 7 years	hazard ratio = 1.37; (95% CI, 1.19-1.59), hazard ratio = 1.29; (95% CI, 1.15-1.44), risk ratio = 1.13; (95% CI, 1.01-1.27)
Liew et al.,2016b	First-trimester APAP use	Poorer attention scores in childhood (-0.34, -0.63, -0.05 for overall attention; -0.25, -0.50, -0.01 for selective attention)	Not reported
Liew et al.,2016b	Prenatal exposure to APAP	Subnormal overall attention, selective attention difficulties, or parent-rated subnormal executive function (metacognition index)	OR 1.5, 95% CI 1.0-2.5; OR 1.5, 95% CI 1.0-2.4; OR 1.5, 95% CI 0.9-2.3
Liew et al.,2019	APAP use at the time of pregnancy	Childhood ADHD	OR = 1.34, 95% CI: 1.05-1.72
Thompson et al.,2014	APAP use during pregnancy	Higher total scores on all 3 SDQ formats	Not reported
Ystrom et al.,2017	Maternal APAP use for all indications, for more than 29 days	ADHD diagnosis	HR of 2.20 (95% CI 1.50-3.24)
Ystrom et al.,2017	APAP use for fever and infections, for 22 to 28 days	ADHD diagnosis	HR = 6.15 (95% CI 1.71-22.05)

Anand 2021:

- Cord blood acetaminophen >50th percentile was associated with higher odds of ADHD diagnosis (aOR: 2.10, 95% CI 1.43, 3.11).

Baker 2020:

- Detection of acetaminophen in meconium was associated with increased odds of ADHD (OR = 2.43, 95% CI, 1.41-4.21) and negative brain connectivity.
- A dose-response association was detected; each doubling of exposure increased the odds of ADHD by 10% (OR = 1.10, 95% CI 1.02-1.19).

Chen 2019:

- Acetaminophen exposure in the second trimester (OR = 1.19, 95% CI 1.00-1.40), first and second trimester (OR = 1.28, 95% CI 1.00-1.64), or any trimester (OR = 1.20, 95% CI 1.01-1.42) was associated with an increased risk of ADHD in offspring.

Ji 2018:

- Below median and above median levels of maternal acetaminophen burden were associated with a 58% and 88% increase in the odds of ADHD diagnosis, respectively (Model 6: OR for below median = 1.58, 95% CI 1.02-2.46; OR for above median 1.88, 95% CI 1.18, 3.00).

Gustavson 2021:

- Long-term exposure (29 days or more) to acetaminophen during pregnancy was associated with a two-fold increase in risk of ADHD diagnosis (aHR = 2.02, 95% CI = 1.17–3.25).
- In the sibling control model, the association between long-term acetaminophen use and ADHD in the child was no longer present (aHR = 1.06, 995% CI = 0.51–2.05).

Liew et al.,2014:

- Maternal acetaminophen use during pregnancy was associated with a higher risk of children receiving a hospital diagnosis of HKD (hazard ratio = 1.37; 95% CI, 1.19-1.59), use of ADHD medications (hazard ratio = 1.29; 95% CI, 1.15-1.44), or having ADHD-like behaviors at age 7 years (risk ratio = 1.13; 95% CI, 1.01-1.27).
- The associations were stronger with use in multiple trimesters and showed an exposure-response trend with increasing frequency of acetaminophen use during gestation.

Liew et al.,2016b:

- First-trimester APAP use was associated with poorer attention scores in childhood (mean difference -0.34, 95% CI -0.63, -0.05 for overall attention; -0.25, 95% CI -0.50, 0.01 for selective attention).
- Prenatal exposure to APAPl increased the risk of subnormal overall attention (OR 1.5, 95% CI 1.0-2.5), selective attention difficulties (OR 1.5, 95% CI 1.0-2.4), and parent-rated subnormal executive function (metacognition index, OR 1.5, 95% CI 0.9-2.3).
- Longer duration of APAP use in pregnancy further elevated the risks for subnormal overall attention or executive function.

Liew et al.,2019:

- Only APAP use at the time of pregnancy was associated with childhood ADHD (OR = 1.34, 95% CI: 1.05-1.72), and the effect estimates for the two negative control exposure periods (about 4 years before and 4 years after the pregnancy) were null.

Thompson et al.,2014:

- There were significantly higher total scores on all 3 SDQ formats is APAP was used during pregnancy, but there were no significant differences associated with any of the other drugs.

Ystrom et al.,2017:

- Maternal APAP use for all indications, for more than 29 days had a higher HR of 2.20 (95% CI 1.50-3.24).
- APAP use for fever and infections, for 22 to 28 days showed a strong and significant association with ADHD (HR = 6.15; 95% CI 1.71-22.05).

C. APAP and Adverse Birth Outcomes

In the section I review studies that investigated whether APAP use during pregnancy was associated with children having impaired learning, cognitive, or social outcomes (i.e., symptoms found in children diagnosed with ASD or ADHD).

Bertoldi 2020 (~)

The study is an observational study that estimates associations of prenatal and early-life exposure to acetaminophen in early childhood with cognitive, motor, and language skills in two birth cohorts.[437]

Information used to determine exposure: The study used questionnaires to determine acetaminophen use during pregnancy (Project Viva and Pelotas) and infancy (Project Viva).

Outcome definition and determination: The outcomes examined were cognitive, motor, and language skills in early childhood. The American Project Viva cohort assessed cognition at approximately 3 years using the Peabody Picture Vocabulary Test and the Wide Range Achievement of Visual Motor Abilities (WRAVMA). The Brazilian 2015 Pelotas Birth Cohort assessed cognition at 2 years using the INTERGROWTH-21st Neurodevelopment Assessment.

Control group: The control group would be children who were not exposed to acetaminophen during pregnancy or infancy.

Study size: The study included 1217 mother-child pairs from the American Project Viva cohort enrolled between 1999-2002 and 3818 mother-child pairs from the Brazilian 2015 Pelotas Birth Cohort.

Confounding factors or biases and how or if they were controlled: The study used linear regression to estimate associations of acetaminophen use during pregnancy (Project Viva and Pelotas) and infancy (Project Viva) with children's cognitive scores adjusted for maternal age, pre-pregnancy body mass index,

[437] Bertoldi et al. Associations of acetaminophen use during pregnancy and the first year of life with neurodevelopment in early childhood. Paediatr Perinat Epidemiol. 2020 May;34(3):267-277. doi: 10.1111/ppe.12632. Epub 2020 Jan 22. PMID: 31965601; PMCID: PMC7192774.

education, parity, race/ethnicity, smoking and alcohol use during pregnancy, depression during pregnancy, antibiotic and ibuprofen use during pregnancy, household income, and child's sex.

Limitations: The authors reported differences in outcomes and exposures between the Pelotas and Viva cohorts, making it challenging to ensure consistency in the findings. There was also a lack of information regarding dose and timing of exposures, and potential under-reporting in self-reported questionnaires or interviews. Confounding by indication was a concern, but adjustments were made for related variables. The cognitive/motor function tests used may be influenced by parental education and cultural/family aspects not accounted for. Differences in baseline covariates between participants and those lost to follow-up were observed, but analyses using inverse probability weighting (IPW) yielded similar results, suggesting minimal bias from loss to follow-up.

Results: In Project Viva, exposure to APAP in both the 1st and 2nd trimester of pregnancy was associated with lower WRAVMA drawing scores (β −1.51, 95% CI −2.92, −0.10). In Pelotas, exposure to APAP in both the 1st and 2nd trimester of pregnancy was not associated with INTER-NDA motor scores (β 0.02; 95% CI −0.05, 0.09) and was associated with higher INTER-NDA total scores (β 0.08, 95% CI 0.01, 0.16). Other comparisons did not show significant associations.

The study concluded that inconsistencies and lack of specificity of the findings did not clarify the research question considering that there is still a large variability and uncertainty to define the risk or safety in the use of acetaminophen related to cognition in early childhood. More studies using better exposure assessment and better confounding variables are needed to clarify these associations.

Bornehag 2018

The study is an observational population-based pregnancy cohort study.[438]

Information used to determine exposure: The study used two measures of exposure: (1) maternally reported number of APAP tablets taken between conception and enrollment; (2) APAP urinary concentration at enrollment.

Outcome definition and determination: The outcome examined was language development at 30 months, assessed by a nurse's evaluation and a parental questionnaire, including the number of words the child used (<25, 25–50, and >50). The main study outcome was parental report of use of fewer than 50 words, termed language delay (LD).

Control group: The control group would be children without language delay.

Study size: The study included 754 women who enrolled in the Swedish Environmental Longitudinal, Mother and child, Asthma and allergy (SELMA) study in pregnancy week 8–13.

Confounding factors or biases and how or if they were controlled: The study adjusted for maternal weight, mother's education, smoking, and week of enrollment.

[438] Bornehag et al. Prenatal exposure to acetaminophen and children's language development at 30 months. Eur Psychiatry. 2018 Jun;51:98-103. doi: 10.1016/j.eurpsy.2017.10.007. Epub 2018 Jan 10. PMID: 29331486.

Limitations: Reported limitations by the authors included unmeasured confounding, but they indicated that previous research and adjustments for potential confounders suggest that confounding by indication is unlikely. Exposure misclassification was a concern, as both urinary biomarkers and self-reported measures may underestimate exposure towards the null. Additionally, environmental sources of APAP may contribute to exposure variability. Outcome misclassification was a concern, although the validity of the language development instrument used is supported by consistent results from another study. They also reported that the study had limited power due to the small number of participants and low prevalence of language delay.

Results: The adjusted odds ratio (OR) for LD among girls whose mothers reported >6 vs. 0 APAP tablets was 5.92 (95% confidence interval (CI) 1.10–31.94). The OR for LD in girls whose mothers' urinary APAP was in the highest compared to the lowest quartile was 10.34 (95% CI 1.37–77.86).

Overall, the study reported that both the number of APAP tablets and urinary APAP concentration were associated with greater LD in girls but not in boys. The study concluded that given the prevalence of prenatal APAP use and the importance of language development, these findings, if replicated, would suggest that pregnant women should limit their use of this analgesic during pregnancy.

Brandlistuen 2013
The study is a sibling-controlled cohort study.

Information used to determine exposure: The study used maternal self-reported use of paracetamol during pregnancy. This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: The outcomes examined were cognitive, motor, and language skills in early childhood. The study assessed cognition at 3 years using the McCarthy Scales of Children's Abilities, behavior at 5 years using the Strengths and Difficulties Questionnaire, and gross motor development at 3 years using the Ages and Stages Questionnaire.

Control group: The control group would be children who were not exposed to paracetamol during pregnancy.

Study size: The study included 48,631 children from the Norwegian Mother and Child Cohort Study (MoBa) whose mothers returned the 3-year follow-up questionnaire by May 2011. Within this sample were 2919 same-sex sibling pairs who were used to adjust for familial and genetic factors. Among the 2919 pairs of siblings with complete data on paracetamol exposure: 134 (4.6%) were discordant for exposure >28 days; 805 (27.6%) were discordant for 1–27 days of exposure; and 1980 were concordant (1224 were both unexposed, 756 were both exposed).

Confounding factors or biases and how or if they were controlled: The study adjusted for a number of factors, including maternal age, education, smoking, alcohol use, caffeine intake, pre-pregnancy body mass index (BMI), parity, marital status, household income, life events during pregnancy, symptoms of depression/anxiety during pregnancy, use of other pain medication during pregnancy, fever/infection during pregnancy, child sex, gestational age at birth, birth weight, and breastfeeding duration.

Limitations: Reported limitations included the relatively low participation rate in the MoBa study and selection bias. Reliance on self-reporting for assessment could lead to underestimation due to social desirability and stigma. The study was unable to consider dosage and distinguish between continuous and sporadic APAP use during pregnancy due to limited data. There was also a possibility of residual confounding factors, such as unreported infections or illnesses, influencing the observed effects.

Results: The study reported that children exposed to prenatal APAP for more than 28 days had poorer gross motor development (β 0.24), communication (β 0.20), externalizing behavior (β 0.28), internalizing behavior (β 0.14), and higher activity levels (β 0.24) compared with unexposed children. Children exposed prenatally to short-term use of APAP (1–27 days) also had poorer gross motor outcomes (β 0.10), but the effects were smaller than with long-term use.

Overall, the study concluded that children exposed to long-term use of APAP during pregnancy may be at increased risk of neurodevelopmental disorders.

Golding 2019 (~)
The study is a longitudinal cohort study.[439]

Information used to determine exposure: The study used data collected by the Avon Longitudinal Study of Parents and Children (ALSPAC) at 32-weeks gestation and referring to the period from 18 to 32 weeks, which identified 43.9% of women having taken paracetamol.

Outcome definition and determination: The outcomes examined were neurocognitive outcomes in the child, including behavior, language, and cognitive development.

Control group: The control group would be children whose mothers did not take paracetamol during pregnancy.

Study size: The study included data from the ALSPAC cohort, which recruited over 14,000 pregnant women with expected delivery dates between April 1991 and December 1992.

Confounding factors or biases and how or if they were controlled: The study used an exposome analysis first to determine the background factors associated with pregnant women taking paracetamol, and then allowed for those factors to assess associations with child outcomes. The study identified 15 variables independently associated with taking paracetamol in this time period, which were used as potential confounders.

Limitations: Reported limitations included collection constraints, potentially leaving out other important confounding factors that could impact the conclusions. Additionally, the approach used to identify confounders was stringent, and relaxing the selection criteria may have revealed a wider range of confounding variables. The examination of APAP use was limited to the period between 18 and 32 weeks

[439] Golding et al. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: A longitudinal cohort study. Paediatr Perinat Epidemiol. 2020 May;34(3):257-266. doi: 10.1111/ppe.12582. Epub 2019 Sep 15. PMID: 31523834; PMCID: PMC7217049.

of pregnancy, excluding early and late stages. The available data on the frequency of APAP use were insufficient, particularly for analyzing frequent users. The analysis also focused on continuous data for the outcomes considered, potentially missing strong or dose effects that may be present in the tails of the distribution.

Results: Adjusted finding identified 12 independent associations with APAP use at $P < .05$, four of which were at $P < .0001$ (all related to child behaviors reported by the mother at 42 and 47 months, *e.g.*, conduct problems: adjusted mean score +0.22 (95% confidence interval 0.10-0.33). These findings included measures of hyperactivity, attention, conduct problems, and total behavioral difficulties, mostly in the pre-school period.

Overall, the study reports that of 135 neurocognitive variables considered, adjusting for the likelihood of false discovery, the study identified 56 outcomes for adjusted analyses. The study concluded that if paracetamol use in mid-to-late pregnancy has an adverse effect on child neurocognitive outcome, it appears to mainly relate to the pre-school period.

Laue 2019 (~)
The study is a prospective birth cohort study.[440]

Information used to determine exposure: The study used concentrations of acetaminophen measured in meconium, which more objectively captures exposure of the fetus than maternal report.

Outcome definition and determination: The outcomes examined were neurocognitive development in early childhood, including cognitive, motor, and language skills. At age 6-8 years, children completed a set of subtests from the Wechsler Intelligence Scale for Children, 4th edition.

Control group: The control group would be children who were not exposed to acetaminophen during pregnancy.

Study size: The study included data from the GESTE cohort, which recruited pregnant women in Canada. Women were recruited between 2007 and 2009 during the first trimester of pregnancy and at delivery (n = 800). At age 6–8 years, 363 children completed a series of neurocognitive tests at the study site, 195 of whom had stored meconium. After excluding individuals with missing covariate data, the final sample size was 118 children.

Confounding factors or biases and how or if they were controlled: The study adjusted for a number of factors, including maternal age, education, smoking, alcohol use, pre-pregnancy body mass index (BMI), parity, marital status, household income, life events during pregnancy, symptoms of depression/anxiety during pregnancy, use of other pain medication during pregnancy, fever/infection during pregnancy, child sex, gestational age at birth, birth weight, and breastfeeding duration.

Limitations: The study was small, having only 118 children. Based on exposed (n=63) versus unexposed (n = 55), the study size is currently only powered to measure a ~7-fold increase in risk between two groups.

[440]Laue et al. Association Between Meconium Acetaminophen and Childhood Neurocognitive Development in GESTE, a Canadian Cohort Study. Toxicol Sci. 2019 Jan 1;167(1):138-144. doi: 10.1093/toxsci/kfy222. PMID: 30202886; PMCID: PMC6317422.

To detect a two-fold increase in risk, n = 1608, assuming 1 in 36 background incidence, a = 0.05 and power = 80%.

Results: In those exposed, with APAP in the meconium, the median concentration was 59.9 ng/g. Exposure was categorized into 3 levels: below the analytical limit of detection (≤ LOD, n = 55), low (> LOD, ≤ 59.9 ng/g, n = 32), and high (> 59.9 ng/g, n = 31). The effect of *in utero* APAP exposure on the Coding subtest was marginally significantly different among boys and girls, with girls performing significantly better on the task with higher levels of acetaminophen compared with girls with undetectable levels of exposure (βgirls, low = 2.83 [0.97, 4.70], βgirls, high = 1.95 [-0.03, 3.93], βboys, low = .02 [-1.78, 1.81], βboys, high = -.39 [-2.09, 1.31], interaction = .06). Effect modification by child sex was not observed on other subtests. The study concluded that these results do not support prior reports of adverse neurodevelopmental effects of *in utero* exposure to acetaminophen.

Overall, in fully adjusted models, *in utero* exposure to acetaminophen was not statistically significantly associated with decreased scores on any of the examined subtests in all children combined (n = 118).

Liew 2016a
The study is a prospective cohort study.[441]

Information used to determine exposure: The study used maternal self-reported acetaminophen use during pregnancy, which was assessed prospectively via 3 telephone interviews. This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: The outcome examined was child IQ at age 5. Child IQ was assessed using the Wechsler Primary and Preschool Scales of Intelligence-Revised (WPPSI-R) administered by trained psychologists.

Control group: The control group would be children whose mothers did not use acetaminophen during pregnancy.

Study size: The study included data from 1,491 mothers and children enrolled in the Danish National Birth Cohort (DNBC; 1996-2002).

Confounding factors or biases and how or if they were controlled: The study employed linear regression analysis, adjusting for maternal IQ and other confounding factors, and assessed interactions between acetaminophen and indications for use.

Limitations: There was the potential for exposure misclassification, residual confounding, and lack of generalizability to less healthy children or different populations.

Results: The study reported that both maternal fever in pregnancy and acetaminophen use were associated with child IQ. Children born to mothers using acetaminophen without reporting fever scored on average 3.4 points lower on performance IQ compared with offspring of mothers who neither experienced fever

[441] Liew et al. Prenatal Use of Acetaminophen and Child IQ: A Danish Cohort Study. Epidemiology. 2016 Nov;27(6):912-8. doi: 10.1097/EDE.0000000000000540. PMID: 27479646.

nor took acetaminophen. Exposures for more than one trimester impacts IQ (mean difference = -3.1, 95% CI -5.7 to -0.45). Use from 1-5 week are impacts IQ (mean difference = -3.1, 95% CI -5.6 to -0.68)

The study concluded that maternal acetaminophen use during pregnancy was associated with lower performance IQ in 5-year-olds.

Parker 2019 (~)
The study is a longitudinal study.[442]

Information used to determine exposure: The study used maternal self-reported acetaminophen use during pregnancy, which was assessed via a standardized maternal interview completed 1 year after delivery on average. This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: The outcomes examined were childhood behavior problems at ages 6-12 years. Measures of childhood behavior were obtained via mother- and teacher-report, using the Child Behaviour Checklist and Teacher Report Form.

Control group: The control group would be children whose mothers did not use acetaminophen during pregnancy.

Study size: The study included data from 560 mother-child pairs with data on illnesses and medication use during pregnancy and neurodevelopmental assessments during childhood.

Confounding factors or biases and how or if they were controlled: The study employed linear and log-binomial models to calculate adjusted mean differences (MD) and risk ratios (RR), respectively, for internalizing, externalizing, and total behavior problems comparing acetaminophen users to non-users. Stabilized inverse probability weights were used to account for loss to follow-up, and adjustments for indication were made.

Limitations: The limitations of the study include retrospective self-reported measures of APAP exposure, a focus on the first 5 months of pregnancy, potential inaccuracies in medication reporting with longer interview intervals, possible dependent misclassification, and the lack of data on important confounders such as maternal stress, IQ, and behavioral problems.

Results: Approximately 60% (n = 354) of women reported use of APAP during pregnancy. Acetaminophen use during pregnancy was associated with increased total behavior problem scores and a higher risk of clinical behavior problems according to mother reports (MD 2.2, 95% CI 0.3, 4.1 and RR 1.93, 95% CI 0.99, 3.76), but not according to teacher reports. Weighting for participation and adjusting for indications of APAP use had minimal impact on the associations, with attenuated effects on mother-reported behavior problem scores and risk of clinical behavior problems (MD 0.1, 95% CI −2.1, 2.3 and RR 1.31, 95% CI 0.67, 2.58).

[442] Parker et al. Maternal acetaminophen use during pregnancy and childhood behavioural problems: Discrepancies between mother- and teacher-reported outcomes. Paediatr Perinat Epidemiol. 2020 May;34(3):299-308. doi: 10.1111/ppe.12601. Epub 2019 Nov 6. PMID: 31693212; PMCID: PMC7192789.

The study concluded that APAP use during pregnancy was weakly associated with mother-reported behavior problems and not associated with teacher-reported problems.

Rifas-Shiman 2019 (~)
The study is a longitudinal study.[443]

Information used to determine exposure: The study used maternal self-reported acetaminophen and ibuprofen use during pregnancy and infancy, which was assessed via questionnaires. This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: The outcomes examined were childhood executive function and behavior problems at ages 6-12 years. Measures of childhood behavior were obtained via parent- and teacher-report, using the Behavior Rating Inventory of Executive Function (BRIEF) and the Strengths and Difficulties Questionnaire (SDQ), with higher scores indicating worse functioning for both.

Control group: The control group would be children whose mothers did not use acetaminophen or ibuprofen during pregnancy or infancy.

Study size: The study included data from 1,225 mother-child pairs from Project Viva, a pre-birth cohort study.

Confounding factors or biases and how or if they were controlled: The study examined associations of acetaminophen and ibuprofen use during pregnancy and infancy with mid-childhood neurobehavioral outcomes using linear regression models adjusted for potential confounders.

Limitations: Reported limitations included imprecise dose information, limited assessment of analgesic intake during specific pregnancy periods, lack of data on analgesic use during lactation, potential residual confounding by indication, and differences in baseline covariates between participants and those lost to follow-up.

Results: the study reports that during pregnancy, 46.1% of mothers used acetaminophen ≥10 times and 18.4% used any ibuprofen. In the first year, 65.3% and 39.6% of infants received acetaminophen and ibuprofen ≥6 times, respectively. Higher (≥10 vs <10 times) prenatal acetaminophen (β 1.64 points; 95% confidence interval [CI] 0.59, 2.68) and any ibuprofen (β 1.56, 95% CI 0.19, 2.92) were associated with higher parent-rated BRIEF global scores. Infancy exposure (≥6 vs <6 times) to acetaminophen (β 1.69, 95% CI 0.51, 2.87) and ibuprofen (β 1.40, 95% CI 0.25, 2.55) were associated with higher parent-rated BRIEF GEC scores but associations with teacher-rated scores were weaker.

The study concluded that prenatal and early-life exposure to APAP and ibuprofen were associated with poorer executive function and behavior in childhood. These findings highlight the need for further research on the mechanisms through which analgesics may act on fetal and child brain development.

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[443] Rifas-Shimanet al. Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. Paediatr Perinat Epidemiol. 2020 May;34(3):287-298. doi: 10.1111/ppe.12596. Epub 2019 Oct 21. PMID: 31637744; PMCID: PMC7170759.

Stergiakouli 2016
The study was a prospective birth cohort study.[444]

Information used to determine exposure: Acetaminophen use was assessed by questionnaire completion at 18 and 32 weeks of pregnancy and when the child was 61 months old.

Outcome definition and determination: The main outcome was maternal reports of behavioral problems using the Strengths and Difficulties Questionnaire (SDQ) when the children were 7 years old.

Control group: The control group consisted of children whose mothers did not report acetaminophen use during pregnancy.

Study size: The study included 7,796 mothers enrolled in the Avon Longitudinal Study of Parents and Children (ALSPAC) between 1991 and 1992 along with their children and partners.

Confounding factors or biases and how or if they were controlled: The study adjusted for maternal postnatal or partner's acetaminophen use in the analysis.

Limitations: Limitations of the study include the lack of information on indications, dosage, and duration of APAP use, absence of genetic data from partners, limited explanatory power of polygenic risk scores, reliance on maternal reports introducing potential bias, and delayed collection of postnatal acetaminophen use data.

Results: Maternal prenatal acetaminophen use at 18 and 32 weeks of pregnancy was associated with increased odds of conduct problems, hyperactivity symptoms, emotional symptoms, and total difficulties in offspring. The risk ratios (RR) for conduct problems and hyperactivity symptoms were 1.42 (95% CI, 1.25-1.62) and 1.31 (95% CI, 1.16-1.49), respectively. APAP use at 32 weeks was also associated with higher odds of emotional symptoms (RR, 1.29; 95% CI, 1.09-1.53) and total difficulties (RR, 1.46; 95% CI, 1.21-1.77). There was no association found with maternal postnatal or paternal/partner APAP use.

The study concluded that children exposed to acetaminophen prenatally are at increased risk of multiple behavioral difficulties.

Tovo-Rodrigues 2020
The study was a prospective longitudinal study that used data from the 2004 Pelotas Birth Cohort, Brazil.[445]

[444] Stergiakouli et al. Association of Acetaminophen Use During Pregnancy With Behavioral Problems in Childhood: Evidence Against Confounding. JAMA Pediatr. 2016 Oct 1;170(10):964-970. doi: 10.1001/jamapediatrics.2016.1775. PMID: 27533796; PMCID: PMC5300094.
[445] Tovo-Rodrigues et al. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. Paediatr Perinat Epidemiol. 2020 May;34(3):278-286. doi: 10.1111/ppe.12649. Epub 2020 Mar 20. PMID: 32196712.

Information used to determine exposure: Maternal use of medication during pregnancy was retrospectively assessed using a standardized questionnaire applied at the perinatal evaluation. Acetaminophen use was defined as at least once during pregnancy, regardless of the dose used.

Outcome definition and determination: The outcomes were low neurodevelopmental performance at 24 months and emotional/behavioral problems at 48 months of life in children from the 2004 Pelotas Birth Cohort (Brazil). Neurodevelopment was evaluated at 24 months using Battelle's Developmental Inventory (BDI) and behavioral/emotional problems were assessed at 48 months using the Child Behaviour Checklist (CBCL).

Control group: The control group consisted of children whose mothers did not report acetaminophen use during pregnancy.

Study size: At 24 months, a total of 3,727 children had valid information for acetaminophen exposure and BDI, and at 48 months, the number of children with valid information for exposure and CBCL was 3,624.

Confounding factors or biases and how or if they were controlled: The study adjusted for several family and maternal sociodemographic and health factors, medication use during pregnancy, and the sex of the child in their analysis.

Limitations: Reported limitations included retrospective data collection may have led to recall difficulties and underreporting of acetaminophen use during pregnancy; the study may have lacked sufficient power; confounding by indication and residual confounding are possible; postnatal acetaminophen exposure was not assessed.

Results: Prenatal acetaminophen exposure did not show any association with neurodevelopmental performance at 24 months or emotional and behavioral problems at 48 months, as assessed by the BDI and CBCL measures, respectively, in the adjusted models.

The authors conclude that they cannot confirm the existence of an association between acetaminophen used during pregnancy and low neurodevelopmental performance at 24 months and emotional/behavioral problems at 48 months of life based on their results.

Tronnes 2019

The study is a prospective cohort study using data from the Norwegian Mother and Child Cohort Study.[446]

Information used to determine exposure: The exposure was determined by self-reported maternal use of paracetamol during pregnancy, as reported in questionnaires. This is a study limitation, because self-reported maternal APAP use during pregnancy may be subject to recall bias or measurement error.

Outcome definition and determination: The outcomes were parent-reported communication skills, behavior, and temperament in preschool-aged children, assessed using standardized questionnaires.

[446] Trønnes et al. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. Paediatr Perinat Epidemiol. 2020 May;34(3):247-256. doi: 10.1111/ppe.12568. Epub 2019 Aug 25. PMID: 31448449; PMCID: PMC8285062.

Control group: The control group consisted of children whose mothers did not report paracetamol use during pregnancy.

Study size: The study included 32,934 children.

Confounding factors or biases and how or if they were controlled: The study used inverse probability weights and robust standard errors to control for potential confounders such as maternal age, education, marital status, pre-pregnancy BMI, smoking habits, alcohol use, symptoms of anxiety and depression, maternal health conditions during pregnancy, and concomitant medication use.

Limitations: Study limitations include low participation rates with potential self-selection bias, reliance on parent-reported data introducing misclassification, and lack of information on formulation and dose of acetaminophen.
Results: In our study of 32,934 children, prenatal exposure to paracetamol varied across trimesters: 25.4% in one trimester, 15.1% in two trimesters, and 5.4% in all three trimesters. Exposure in two trimesters was associated with lower shyness scores (β −0.62, 95% CI −1.05 to −0.19), while exposure in three trimesters increased the risk of internalizing behavior problems (RR 1.36, 95% CI ,1.02-1.80) and borderline externalizing behavior problems (RR 1.22, 95% CI, 0.93-1.60). Exposure in the second and third trimesters was also linked to lower shyness scores (β −0.32, 95% CI −0.66 to 0.02). Sensitivity analyses highlighted the potential influence of unmeasured confounders biasing the effect estimates.

The authors conclude that an association was found between APAP use in multiple trimesters and lower shyness and greater internalizing behavior in preschool-aged children. They also suggest that chance or unmeasured confounding cannot be ruled out as possible explanations for these findings.

Vlenterie 2016
The study was a prospective cohort study using data from the Norwegian Mother and Child Cohort Study.[447]

Information used to determine exposure: Paracetamol use was classified into short-term (< 28 days) and long-term (≥ 28 days) of exposure.

Outcome definition and determination: The outcomes were communication problems and delayed motor milestone attainment among children at 18 months of age.

Control group: The control group consisted of children whose mothers did not report paracetamol use during pregnancy.

Study size: Of the 51,200 pregnancies included in the study, 40.5% of mothers (n = 20,749) used paracetamol at least once during pregnancy.

[447] Vlenterie et al. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. Int J Epidemiol. 2016 Dec 1;45(6):1998-2008. doi: 10.1093/ije/dyw192. PMID: 27585674; PMCID: PMC5841617.

Confounding factors or biases and how or if they were controlled: The study applied propensity score (PS) matching to examine associations between prenatal paracetamol exposure and neurodevelopmental problems among children at 18 months of age.

Limitations: Reported limitations included the possibility of selection bias in the study cohort, limited generalizability to women with severe forms of headaches or migraines, inability to include information on severity and type of infections during pregnancy, potential residual confounding by unmeasured variables, increased risk of chance findings due to exploring multiple outcomes, reliance on parent-reported behavior outcomes prone to misclassification, and substantial loss to follow-up at the 18-month questionnaire introducing potential selection bias.

Results: The study reported that in the PS-matched analyses, long-term paracetamol exposure during pregnancy was associated with communication problems [odds ratio (OR): 1.38, 95% CI 0.98–1.95] and delayed motor milestone attainment (OR: 1.35, 95% CI 1.07–1.70). The study did not observe increased risks after short-term exposure. Sensitivity analyses for several indications showed similar effects as the PS-matched analyses, suggesting no confounding by indication.

The study concluded that long-term exposure to paracetamol in utero was associated with modestly increased risks of motor milestone delay and impaired communication skills among children at 18 months.

Weight of the Evidence of the Association of APAP with Other Cognitive or Social Outcomes

Overall, the studies above constitute **some evidence that APAP use in pregnancy causes developmental toxicity.** This is supported by reports of impaired learning, cognitive, or social outcomes in offspring exposed to APAP during pregnancy.

Based on a weight-of-evidence analysis of the studies included in the report, **the evidence for an association between prenatal APAP exposure and adverse neurodevelopmental outcomes in children can be considered moderate.** Several studies have reported significant associations between prenatal APAP exposure and poorer cognitive, motor, language, and behavioral outcomes in children. However, the evidence is not consistent across all studies, and some studies did not find significant associations or found mixed results.

APAP has a moderate association with an increased risk of adverse neurodevelopmental outcomes in children. The data from these above studies are summarized below:

Study	Exposure	Outcome	Measure	Result
Bertoldi 2020	APAP use in both the 1st and 2nd trimester of pregnancy	WRAVMA drawing scores in Project Viva	Beta coefficient	-1.51 (95% CI -2.92, -0.10)
Bornehag 2018	Number of APAP tablets and urinary APAP concentration	Language delay in girls	Odds ratio	5.92 (95% CI 1.10–31.94) and 10.34 (95% CI 1.37–77.86)

Brandlistuen 2013	Prenatal APAP use for more than 28 days	Gross motor development, communication, externalizing behavior, internalizing behavior, and higher activity levels	Beta coefficient	0.24, 0.20, 0.28, 0.14, and 0.24 respectively
Golding 2019	APAP use at P < .05	Child behaviors reported by the mother at 42 and 47 months	Adjusted mean score	+0.22 (95% CI 0.10-0.33) for conduct problems
Laue 2019	In utero APAP exposure on the Coding subtest	Coding subtest scores among boys and girls	Beta coefficient	-0.39 (95% CI -2.09, 1.31) for boys and 1.95 (95% CI -0.03, 3.93) for girls
Liew 2016a	Maternal APAP use without reporting fever	Performance IQ	Mean difference	-3.1 (95% CI -5.7 to -0.45)
Parker 2019	Prenatal APAP exposure	Total behavior problem scores and clinical behavior problems according to mother reports	Mean difference and risk ratio	2.2 points (95% CI ,0.3-4.1) and 1.93 (95% CI ,0.99-3.76) respectively
Rifas-Shiman 2019	Higher prenatal APAP and any ibuprofen	Parent-rated BRIEF global scores	Beta coefficient	1.64 points (95% CI ,0.59-2.68) and 1.56 points (,95% CI ,0.19-2.92) respectively
Stergiakouli 2016	Maternal prenatal APAP use at 18 and 32 weeks of pregnancy	Conduct problems, hyperactivity symptoms, emotional symptoms, and total difficulties in offspring	Risk ratio	at 18 weeks: 1.42 (95% CI, 1.25-1.62) and 1.31 (95% CI, 1.16-1.49), at 32 weeks: RR 1.29 (95% CI, 1.09-1.53) and RR 1.46; (95% CI, 1.21-1.77).
Tovo-Rodrigues2020	Prenatal acetaminophen exposure	Neurodevelopmental performance at 24 months or emotional and behavioral problems at 48months	None	
Tronnes 2019	Exposure in three trimesters	Internalizing behavior problems and borderline externalizing behavior problems	Risk ratio	RR 1.36 (95% CI ,1.02-1.80) and RR 1.22 (95% CI, 0.93-1.60).
Vlenterie 2016	Long-term paracetamol exposure during pregnancy	Communication problems and delayed motormilestone attainment	Odds ratio	OR: 1.35 (95% CI 1.07–1.70).